IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Hickey, E. R. et al	)	Art Unit:	1626
Serial No.:	10/790,549	)	Examiner:	Coppins, Janet L
Conf. No.:	9699	)		
Filed:	03/01/2004			
For:	Cathepsin S Inhibitors			
Docket No.:	9/278			

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ERICK YOUNG, UNDER 37 CFR 1.132

Sir:

I, Erick Young, solemnly state and declare as follows:

1. My technical background is as follows: I am a trained organic chemist having received a Bachelor of Science degree in ACS Chemistry from Ohio Northern University in 1991 and a Ph.D. degree in Chemistry from The Pennsylvania State University in 1996.

I engaged in post doctoral studies in synthetic organic chemistry at The Ohio State University from 1996 to 1998 ; I joined Boehringer Ingelheim Pharmaceuticals, Inc. in April 1998 as a [Senior Scientist; and I presently hold the position of Senior Principal Scientist.

2. I am familiar with the subject matter of the above-noted patent application.

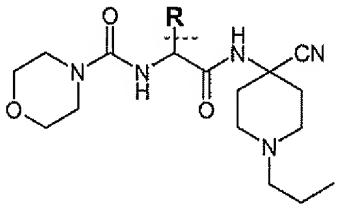
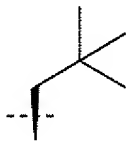
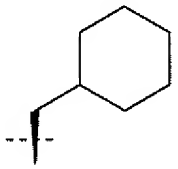
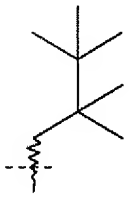
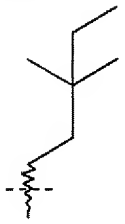
3. I am familiar with the cited prior art document of Emmanuel et al. U.S. Pat. No. 6,420,364.

4. In my capacity of chemistry coordinator I supervised the screening and evaluation of compounds under the research division's program directed to the development of compounds active against Cathepsin S. The novel feature of this invention is the discovery that the specific P2 side chains 3,3-dimethyl pentyl(I), 2,2,3,3-tetramethyl butyl(II), and 3,3-dimethyl butyl(III) substantially improve the selectivity profile of these inhibitors for cathepsin S over its closely related family member cathepsin L. In general, the property of increased selectivity is highly desirable to avoid any potential toxicity associated with inhibition of other protease targets. In particular, mice deficient of Cathepsin L or possessing nonfunctional Cathepsin L, have been

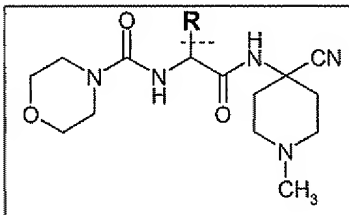
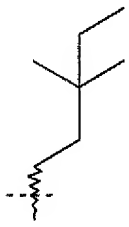
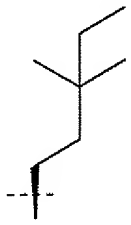
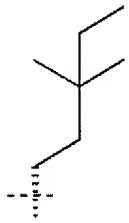
shown to demonstrate numerous undesirable phenotypes including brain atrophy (PNAS USA 2002 99 (12) 7883) progressive cardiomyopathy (PNAS USA 2002 99 (9) 6234), impairment of the male reproductive system (Biology of Reproduction 2003 68 (2) 680), and severe epidermal hyperplasia (American Journal of Pathology 2002 161 (2) 693). All references cited above are attached herewith as Exhibit A.

5. In order to demonstrate the unexpectedly improved selectivity profile of these inhibitors for cathepsin S over its closely related family member cathepsin L, activity for the compounds of the present invention, the assay shown below was performed.

When the following compounds listed in the following table were screened in the Cathepsin S and Cathepsin L Assays described on pages 38 to 40 of the above-noted patent application, the results obtained are shown in the following table:

Compound	Cat S Ki (nM))	Cat L Ki (nM)	Cat L/S
			
 R = (Compound from column 28, lines 43-44 of U.S. Pat. No. 6,420,364 Morpholine-4-carboxylic acid [1-(1-n-propyl-4-cyano-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butyl]-amide)	14	166	12X
 R= (Compound Example 6 of U.S. Pat. No. 6,420,364 Morpholine-4-carboxylic acid [1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl]-amide)	6.5	34	5X
 R = (Compound on page 28 of the above-noted patent application, second compound of example 5: Morpholine-4-carboxylic acid [1-(4-cyano-1-propyl-piperidine-4-ylcarbamoyl)-3,3,4,4-tetramethyl-pentyl]-amide)	32	21,000	656X
 R = (Compound on page 29 of the above-noted patent application last compound of example 5: Morpholine-4-carboxylic acid [1-(4-cyano-1-propyl-piperidine-4-ylcarbamoyl)-4,4-dimethyl-hexyl]-amide)	20	14,900	745X

We have also developed a chiral synthesis for the 3,3-dimethyl pentyl side chain (type I) found on page 9 of the present patent application to confirm the selectivity is indeed attributed to the more active enantiomer

	Cat S Ki (nM)	Cat L Ki (nM)	Cat L/S
	23	10,500	456X
	31	12,500	403X
	15,900	No data	

6. The above-identified results are unexpected, as there is no expectation that particular P2 alkyl group substitution of the claimed invention would improve the selectivity profile of these inhibitors for cathepsin S over its closely related family member cathepsin L.

8. The above-identified results are commensurate in scope for the claimed subject matter, as there is no reason to expect that other compounds bearing these alkyl groups at this position, not to exhibit similar activity.

7. The difference between the improved selectivity profile of the compounds of the present invention and that of the prior art are significant. Accordingly, the consumer would prefer the effective compound of the presently claimed invention.

The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 6/21/07

Signature: _____

Erick Young